(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 November 2003 (20.11.2003)

PCT

(10) International Publication Number
WO 03/095448 A1

(51) International Patent Classification[7]: C07D 401/12, A61K 31/505, A61P 35/00

(21) International Application Number: PCT/US03/13604

(22) International Filing Date: 2 May 2003 (02.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/378,329 6 May 2002 (06.05.2002) US

(71) Applicant *(for all designated States except US)*: **BAYER PHARMACEUTICALS CORPORATION** [US/US]; 400 Morgan Lane, West Haven, CT 06516 (US).

(71) Applicants and
(72) Inventors: **WOOD, Jill, E.** [US/US]; 3007 Ridge Road, North Haven, CT 06473 (US). **CHEN, Yuanwei** [CN/US]; 15 Blue Ridge Lane, North Haven, CT 06473 (US). **CHEN, Jianqing** [CA/US]; 117 Frederick Street, Apt. #2-L, New Haven, CT 06515 (US). **HART, Barry** [US/US]; 555 Middlefield Road, Apt. L306, Mountain View, CA 94043 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LIU, Donglei** [CN/US]; 23 Kenneth Street, Apt. 4-4B, West Haven, CT 06516 (US). **VERMA, Sharad, K.** [US/US]; 29 Harbour Close, New Haven, CT 06519 (US).

(74) Agents: **GREENMAN, Jeffrey, M.** et al.; Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516 (US).

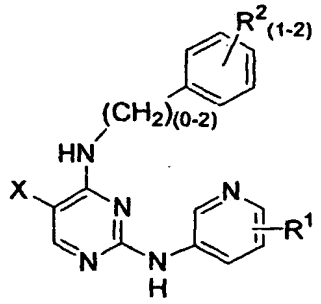
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

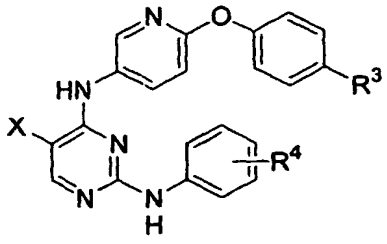
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

[Continued on next page]

(54) Title: PYRIDINYL AMINO PYRIMIDINE DERIVATIVES USEFUL FOR TREATING HYPER-PROLIFERATIVE DISORDERS



I(a)



I(b)

(57) Abstract: The present invention relates to a compound of Formula I(a) or I(b)I(a) I(b)whereinX is halo;R1 is selected from morpholinyl, NHC(O)(C1-C6)alkyl and O-phenyl wherein said phenyl is optionally substituted with a substituent selected from (C1-C6)alkyl, (C1-C6)alkoxy, halo, and CF3;R2 is in each instance independently selected from SO2NH2 and halo;R3 is selected from H, (C1-C6)alkoxy, CF3 and halo;R4 is a substituent selected from C(O)OH, NHC(O)-phenyl, a five membered heterocycle, and imadazo[1,2-a]pyridinyl; or a pharmaceutically acceptable salt thereof.

WO 03/095448 A1

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Pyridinyl Amino Pyrimidine Derivatives Useful For Treating Hyper-Proliferative Disorders

This application claims priority from US provisional application 06/378,329, filed May 6, 2002.

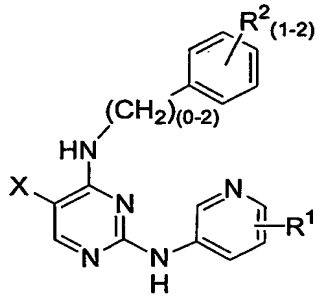
Field of the Invention

This invention relates to novel pyridinyl amino pyrimidine compounds, pharmaceutical compositions containing such compounds, and the use of those compounds and/or compositions for treating hyper-proliferative disorders.

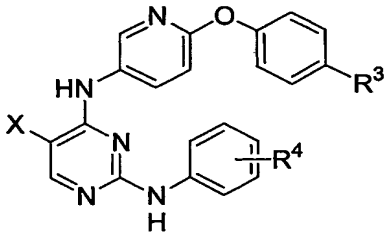
Description of the Invention

Compounds of the Invention

One embodiment of this invention relates to a compound of Formula I(a) or I(b)



I(a)



I(b)

wherein

X is halo;

R^1 is selected from morpholinyl, NHC(O)(C_1-C_6)alkyl and O—phenyl wherein said phenyl is optionally substituted with a substituent selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, and CF_3;

R^2 is in each instance independently selected from SO_2NH_2 and halo;

R^3 is selected from H, (C_1-C_6)alkoxy, CF_3 and halo;

R^4 is a substituent selected from C(O)OH, NHC(O)-phenyl, a five membered heterocycle, and imadazo[1,2-a]pyridinyl;

or a pharmaceutically acceptable salt thereof.

Formula I(a) and Formula I(b) may also be referred to herein severally and collectively as Formula I.

The terms identified above have the following meaning throughout:

The term "optionally substituted" means that the moiety so modified may have from none to up to about the highest number of substituents indicated. When there are two or more substituents on any moiety, each substituent is defined independently of any other substituent and can, accordingly, be the same or different.

The term "(C_1-C_6)alkyl", means linear or branched saturated carbon groups having from about 1 to about 6 C atoms. Such groups include but are not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, and the like.

The term "(C_1-C_6)alkoxy" means a linear or branched saturated carbon group having from about 1 to about 6 C atoms, said carbon group being attached to an O atom. The O atom is the point of attachment of the alkoxy substituent to the pyridyl ring. Such groups include but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, and the like.

The term "halo" means an atom selected from Cl, Br, and F.

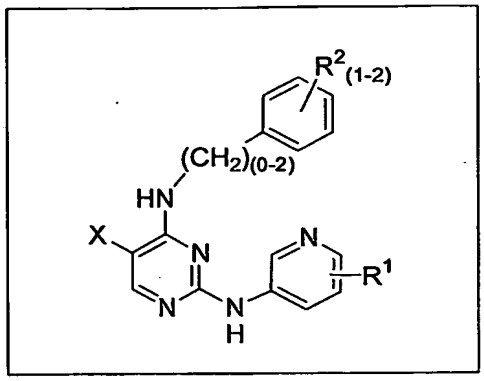
The term "5 memebered heterocycle" means an aryl ring containing 5 atoms, 1, 2, or 3 of which are heteroatoms selected from N, O and S, the rest of the atoms in the ring being C, with the proviso that said ring may contain no more than 1 O atom or 1 S atom. The heteroaromatic ring may be attached to the phenyl ring of the core molecule at any available C or N atom. Examples of such groups include pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, oxadiazole, thiadiazole, and tetrazole in all their possible isomeric forms.

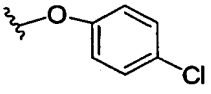
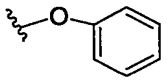
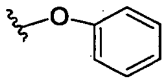
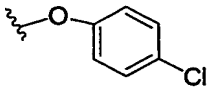
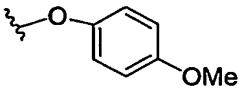
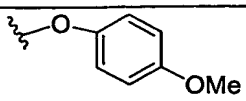
Imidaol[1,2-a]pyridine can be attached to the phenyl ring of the core molecule through any available C on its five-membered ring.

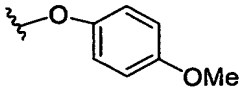
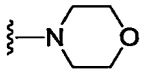
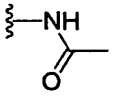
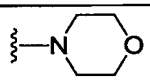
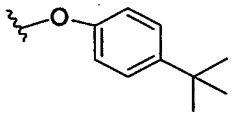
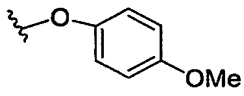
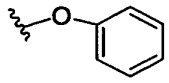
Except where an R group is attached at a specific point of attachment of a phenyl ring (e.g., R^1 and R^3), when a phenyl ring may be substituted with one or more substituent(s), the substituent(s) may be attached to the phenyl ring at any available C atom, preferably at the 3, 4, or 5 C. When there is more than 1 substituent on a phenyl ring, each is selected independently from the other so that they may be the same or different.

Representative compounds of Formula I(a) are shown in Table I.

Table 1



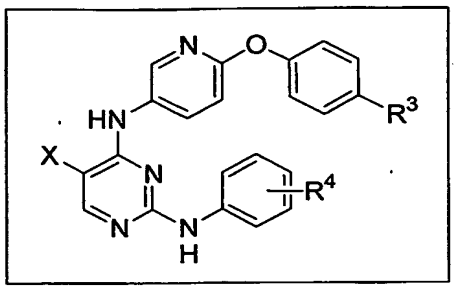
Example	X	$(CH_2)_{(0-2)}$	R^1	R^2	TLC R_f (eluant)
1	Br	0		4-fluoro	$(M+H)^+$ 486.2 t_R 3.83 min TLC Rf 0.77 (50% EtOAc/hex) Mp = 175-176 °C
2	Br	0		4-fluoro	$(M+H)^+$ 452.3 t_R 3.55 min TLC Rf 0.60 (50% EtOAc/hex)
3	Br	0		3, 4-difluoro	$(M+H)^+$ 470.5 t_R 3.13 min TLC Rf 0.72 (50% EtOAc/hex)
4	Br	0		3-fluoro	$(M+H)^+$ 486.6 t_R 3.41 min TLC Rf 0.56 (50% EtOAc/hex)
5	Br	0		4-fluoro	$(M+H)^+$ 484.3 t_R 2.59 min TLC Rf 0.58 (50% EtOAc/hex)
6	Br			3-fluoro	$(M+H)^+$ 482.2 t_R 3.16 min

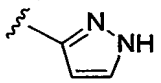
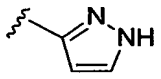
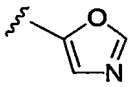
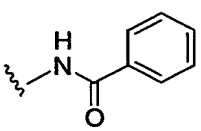
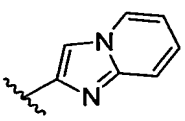
		0			TLC Rf 0.86 (EtOAc) mp = 217-218 °C
7	Br	0		3, 4-difluoro	$(M+H)^+$ 500.5 t_R 3.07 min TLC Rf 0.52 (50% EtOAc/hex)
8	Br	0		4-fluoro	$(M+H)^+$ 445.3 t_R 2.65 min TLC Rf 0.74 (EtOAc)
9	Br	0		4-fluoro	$(M+H)^+$ 416.3 t_R 2.73 min TLC Rf 0.56 (EtOAc)
10	Br	0	4-CF_3	4-fluoro	$(M+H)^+$ 428.2 t_R 2.13 min TLC Rf 0.57 (50% EtOAc/hex)
11	Br	0		4- methoxy	$(M+H)^+$ 459.2 TLC Rf 0.75 (EtOAc)
12	Br	0		4-fluoro	$(M+H)^+$ 508.5 t_R 3.43 min TLC Rf 0.81 (50% EtOAc/hex) mp = > 250 °C
13	Br	2		4-SO_2NH_2	$(M+H)^+$ 571.5 TLC Rf 0.54 (66% EtOAc/34%Hex)
14	Br	2		4-SO_2NH_2	$(M+H)^+$ 543.0 t_R 2.30 min TLC Rf 0.50 (67% EtOAc/hex)

The structure of each compound in Table 1 is consistent with the analytical data (^{1}H NMR and LC-MS) also presented in Table 1.

Representative compounds of Formula I(b) are shown in Table 2.

Table 2



Example	X	R_3	R_4	TLC R_f (eluant)
15	Br	H	3- 	$(M+H)^+$ 500.5 TLC Rf 0.65 (80% EtOAc/ 20% Hex)
16	Br	O-Methyl	3- 	$(M+H)^+$ 530.6 TLC Rf 0.60 (80% EtOAc/ 20% Hex)
17	Br	O-Methyl	3- 	$(M+H)^+$ 533.4 t_R 2.56 min TLC Rf 0.33 (50% EtOAc/ 50% Hex)
18	Br	O-Methyl	4-carboxyl	$(M+H)^+$ 508.1 t_R 2.45 min
19	Br	O-Methyl	4- 	$(M+H)^+$ 583.5 t_R 2.64 min TLC Rf 0.35 (50% EtOAc/ 50% Hex)
20	Br	O-Methyl	4- 	$(M+H)^+$ 580.4 t_R 2.16 min TLC Rf 0.10 (50% EtOAc/ 50% Hex)

The structure of each compound in Table 2 is consistent with the analytical data (^{1}H NMR and LC-MS) also presented in Table 2.

Table 3

IUPAC Names of Compound Examples 1-20

Example	Compound Name*
1	*N*-(5-bromo-2-{[6-(4-chlorophenoxy)-3-pyridinyl]amino}-4-pyrimidinyl)-*N*-(4-fluorophenyl)amine
2	*N*-{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}-*N*-(6-phenoxy-3-pyridinyl)amine
3	*N*-{5-bromo-4-[(3,4-difluorophenyl)amino]-2-pyrimidinyl}-*N*-(6-phenoxy-3-pyridinyl)amine
4	5-bromo-N^2-[6-(4-chlorophenoxy)-3-pyridinyl]-N^4-(3-fluorophenyl)-2,4-pyrimidinediamine hydrochloride
5	*N*-{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}-*N*-[6-(4-methoxyphenoxy)-3-pyridinyl]amine
6	*N*-{5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}-*N*-[6-(4-methoxyphenoxy)-3-pyridinyl]amine hydrochloride
7	5-bromo-N^4-(3,4-difluorophenyl)-N^2-[6-(4-methoxyphenoxy)-3-pyridinyl]-2,4-pyrimidinediamine hydrochloride
8	*N*-{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}-*N*-[6-(4-morpholinyl)-3-pyridinyl]amine trifluoroacetate
9	*N*-[5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-pyridinyl]acetamide trifluoroacetate
10	*N*-{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}-*N*-[4-(trifluoromethyl)-3-pyridinyl]amine hydrochloride
11	5-bromo-N4-(4-methoxyphenyl)-N^2-[6-(4-morpholinyl)-3-pyridinyl]-2,4-pyrimidinediamine trifluoroacetate
12	*N*-(5-bromo-2-{[6-(4-tert-butylphenoxy)-3-pyridinyl]amino}-4-pyrimidinyl)-*N*-(4-fluorophenyl)amine
13	4-{2-[(5-bromo-2-{[6-(4-methoxyphenoxy)-3-pyridinyl]amino}-4-pyrimidinyl)amino]ethyl}benzenesulfonamide hydrochloride
14	4-{2-[(5-bromo-2-{[6-phenoxy-3-pyridinyl]amino}-4-pyrimidinyl)amino]ethyl}benzenesulfonamide hydrochloride
15	*N*-{5-bromo-4-[(6-phenoxy-3-pyridinyl)amino]-2-pyrimidinyl}-*N*-[3-(1*H*-

Example	Compound Name*
	pyrazol-5-yl)phenyl]amine trifluoroacetate
16	*N*-(5-bromo-4-{[6-(4-methoxyphenoxy)-3-pyridinyl]amino}-2-pyrimidinyl)-*N*-[3-(1*H*-pyrazol-5-yl)phenyl]amine trifluoroacetate
17	*N*-(5-bromo-4-{[6-(4-methoxyphenoxy)-3-pyridinyl]amino}-2-pyrimidinyl)-*N*-[3-(1,3-oxazol-5-yl)phenyl]amine hydrochloride
18	4-[(5-bromo-4-{[6-(4-methoxyphenoxy)-3-pyridinyl]amino}-2-pyrimidinyl)amino]benzoic acid hydrochloride
19	*N*-{4-[(5-bromo-4-{[6-(4-methoxyphenoxy)-3-pyridinyl]amino}-2-pyrimidinyl)amino]phenyl}benzamide hydrochloride
20	*N*-{5-bromo-2-[(4-imidazo[1,2-a]pyridin-2-ylphenyl)amino]-4-pyrimidinyl}-*N*-[6-(4-methoxyphenoxy)-3-pyridinyl]amine hydrochloride

*The IUPAC Names were obtained using the ACD/ILab Web service

The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration or (*R,S*) configuration. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form, and a substituent on a double bond may be present in either *Z* or *E* form. It is intended that all such configurations (including enantiomers and diastereomers) are included within the scope of the present invention. Preferred compounds are those with the absolute configuration of the compound of this invention which produces the more desirable biological activity. Separated, pure or partially purified isomers or racemic mixtures of the compounds of this invention are also included within the scope of the present invention.

The use of pharmaceutically acceptable salts of the compounds of Formula I are also within the scope of this invention. The term "pharmaceutically acceptable salt" refers to either inorganic or organic acid or base salts of a compound of the present invention that have properties acceptable for the therapeutic use intended. For example, *see* S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts that are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate,

benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate. The term acid addition salts also comprises the hydrates and the solvent addition forms which the compounds of this invention are able to form. Examples of such forms are, for example, hydrates, alcoholates and the like.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides including benzyl and phenethyl bromides, and others.

Unless the context clearly indicates to the contrary, whenever the term "compounds of this invention," "compounds of the present invention", and the like, are used herein, they are intended to include the chemically feasible pharmaceutically acceptable salts and/or esters as well as all stereoisomeric forms of the referenced compounds.

Method of Making the Compounds of this Invention:

In general, the compounds of this invention may be prepared by standard techniques known in the art and by known processes analogous thereto. The compounds of this invention can be synthesized according to the General Method described further below.

When the following abbreviations are used herein, they have the following meaning:

t-BuOH	*tert*-Butyl alcohol
EtOAc	Ethyl Acetate
Hex	Hexanes
*I*PA	iso-Propyl alcohol
MeOH	Methyl alcohol

NaOAc	Sodium acetate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Unless otherwise stated, the term 'concentrated under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and/or (d) immersion of the plate in a cerium sulfate solution followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

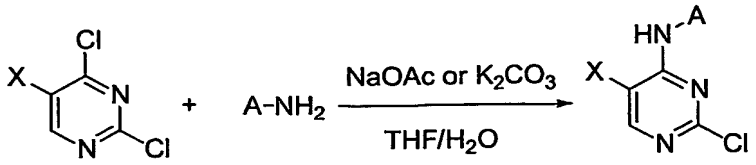
Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric G*N*-Omega 300 (300 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric G*N*-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; d_3-MeOD; δ 49.0; d_6-DMSO δ 39.5) as standard.

HPLC - electrospray mass spectra (HPLC ES-MS) for characterization were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluants were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Preparative HPLC, when needed, was run using either a Gilson 215 Liquid Handler with a Gilson 322 pump and a Gilson UV-VIS-155 detector set at 254 nm or a Shimadzu LC-8A pump with a Shimadzu SPD-10A detector set at 220 nM both equipped with a YMC Pac ProC18 column (150 x 20 mm). Eluant A is acetonitrile with 0.01% of trifluoroacetic acid and Eluant B is water with 0.01% trifluoroacetic acid. Typically, a gradient was run from 10% A / 90% B to 90%A / 10% B over a period of 15-25 min. The fractions of interest were collected and the solvent removed *in vacuo* to give the final compound as a trifluoroacetic acid salt.

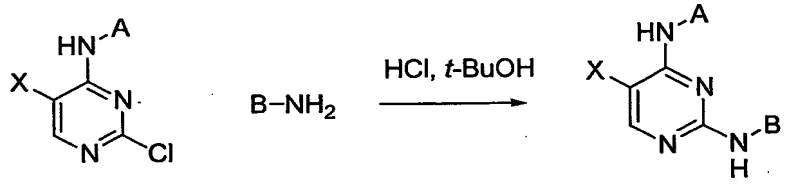
General Method of Preparation of Compounds in Tables 1-2

Step 1.



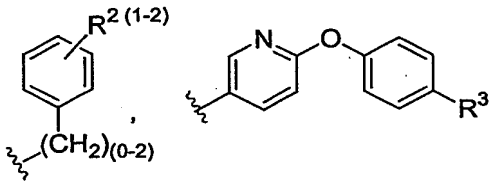
(II) (III) (IV)

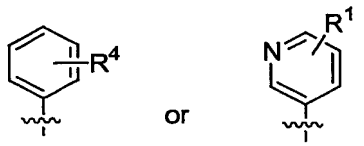
Step 2.



(IV) (V) (I)

where X = F, Br or CF_3;

A = 

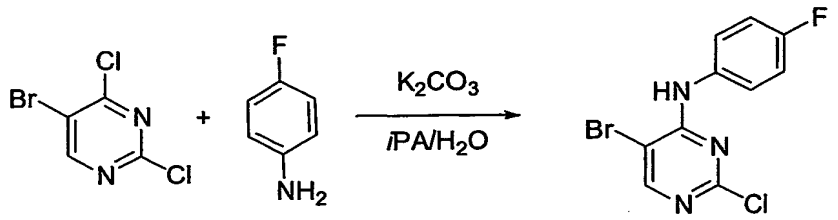
B = 

;

and R^1, R^2, R^3 and R^4 are as illustrated in Examples 1-20 and Tables 1-2.

This general method is described in detail below for certain specific compounds of this invention. The other compounds of this invention identified in Table 1 and Table 2 were prepared in a like manner, starting with the appropriate commercially available or otherwise known or described Formula II, Formula III, and Formula V compounds.

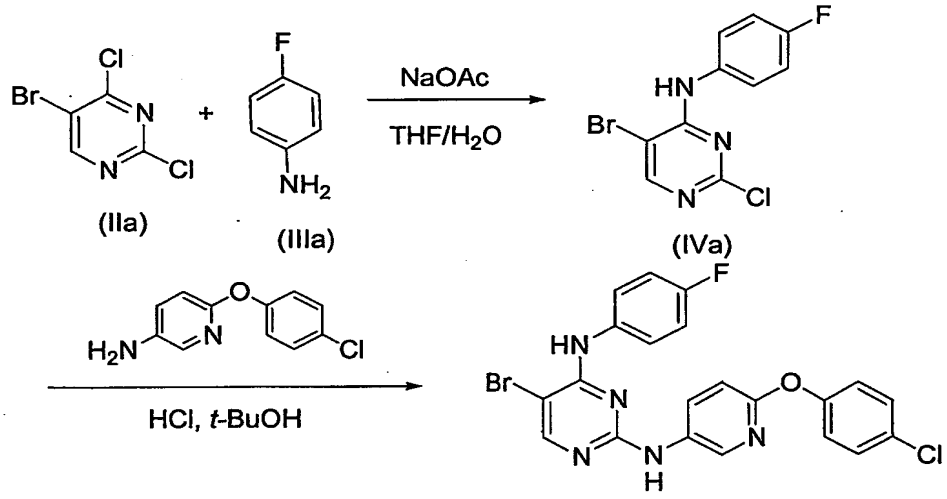
Preparation of 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine



To a solution of K_2CO_3 (44.5 g, 322 mmol) in water (125 mL) and *iso*-propyl alcohol (375 mL), were added 5-bromo-2,4-dichloropyrimidine (25.0 g, 108 mmol) and 4-fluroaniline (12.0g, 107 mmol). The mixture was stirred at room temperature for 18 h then water (3000 mL) was added and the product was precipitated out. The precipitate was filtered and dried to give 30.0 g (90%) 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine as a pale yellow powder.

Example 1

Preparation of *N*-(5-bromo-2-{[6-(4-chlorophenoxy)-3-pyridinyl]amino}-4-pyrimidinyl)-*N*-(4-fluorophenyl)amine



1

Step 1. To a solution of NaOAc (27.0 g, 330 mmol) in water (70 mL) and THF (140 mL) , were added 5-bromo-2,4-dichloropyrimidine (25.0 g, 110 mmol) and 4-fluroaniline (12.2g, 110 mmol). The mixture was stirred at room temperature for 18 h then saturated $NaHCO_3$ solution (50 mL) was added and the aqueous layer was extracted with EtOAc (150 mL × 2); the combined organic layers were dried over $MgSO_4$; filtered and concentrated under reduced pressure. The residue was treated with 200 mL hexane and filtered to give 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine as a 30.0 g pale yellow powder (90%).

Step 2. To a suspension of 5-bromo-2-chloro-4-(4-fluoroanilino)pyrimidine (8.0 g, 26.4 mmol) and 3-amino-5-(4-chlorophenyloxy)pyridine (6.8 g, 26.4 mmol) in t-BuOH (275 mL) was added conc. HCl (1.0 mL). The mixture was heated to 100 °C for 18 h, and then cooled down to room temperature. The precipitate was filtered to give the HCl salt of final product. The HCl salt was suspended in EtOAc (300 mL) and 1 N NaOH (26 mL) and water (200 mL) were added. The mixture was stirred for 10 min until it became clear, and then the layers were separated using a separatory funnel. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, the residue was washed with MeOH and dried *in vacuo* to give 9.0 g (70%) of *N*-(5-bromo-2-{[6-(4-chlorophenoxy)-3-pyridinyl]amino}-4-pyrimidinyl)-*N*-(4-fluorophenyl)amine. R_f 0.77 (1/1 EtOAC/Hex).

Variations of the compounds of the invention can be readily prepared using the processes described above, or by other standard chemical processes known in the art, by employing appropriate starting materials that are readily available and/or are already described herein, as would be known by one skilled in the art.

Generally, a desired salt of a compound of this invention can be prepared in situ during the final isolation and purification of a compound by means well known in the art. For example, a desired salt can be prepared by separately reacting the purified compound in its free base or free acid form with a suitable organic or inorganic acid, or suitable organic or inorganic base, respectively, and isolating the salt thus formed. In the case of basic compounds, for example, the free base is treated with anhydrous HCl in a suitable solvent such as THF, and the salt isolated as a hydrochloride salt. In the case of acidic compounds, the salts may be obtained, for example, by treatment of the free acid with anhydrous ammonia in a suitable solvent such as ether and subsequent isolation of the ammonium salt. These methods are conventional and would be readily apparent to one skilled in the art.

The purification of isomers of a compound of this invention, and the separation of said isomeric mixtures can be accomplished by standard techniques known in the art.

Compositions of the compounds of this invention

The compounds of this invention can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment (including prophylactic treatment) for the particular condition or disease.

Therefore, another embodiment of the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt or ester thereof, of the present

invention.

A pharmaceutically acceptable carrier is any carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated.

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, otically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or

carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate,

or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations which are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is

incorporated herein by reference: Powell, M.F. *et al,* "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* **1998**, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* **1999**, 53(6), 324-349; and Nema, S. *et al,* "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$);

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate);

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection);

chelating agents (examples include but are not limited to edetate disodium and edetic acid);

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate);

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas);

plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures);

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

It is believed that one skilled in the art, utilizing the preceding information, can utilize the present invention to its fullest extent. Nevertheless, the following are examples of pharmaceutical formulations that can be used in the method of the present invention. They are for illustrative purposes only, and are not to be construed as limiting the invention in any way.

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile Injectable Solution

A suitable amount of pure active ingredient is dissolved in sterile, injectable water to a desired concentration, for example from about 1.0 mg/ml to about 50.0 mg/ml. U.S.P. grade sodium chloride crystals (NaCl) is added to the solution such that the final concentration of NaCl is 0.9% by weight of water. The pH of the solution is adjusted to range between approximately pH 2.0 and pH 6.0 by the addition of pure (99.999%purity) hydrochloric acid. The solution is sterilized via filtration through a sterile 0.22 micron filter. The sterile solution is stored in sealed sterile vials wherein each vial contains the desired dosage unit of active ingredient per ml of injection solution.

Sterile Injectable Solution

U.S.P. grade sodium chloride (NaCl) is dissolved in sterile, injectable water to a final concentration of 0.9% NaCl by weight of water. An amount of pure (99.999% purity) hydrochloric acid is added to the NaCl solution to obtain a final pH in the range of approximately pH2.0 to pH6.0. An amount of U.S.P. grade potassium chloride crystals

(KCL) is dissolved in the solution such that the final concentration of KCl is 0.1% by weight. From 0.5 part to about thirty parts by weight of active ingredient (depending on the desired end dosage unit) is added to the solution and is completely dissolved by agitation. The pH of the solution is adjusted again to between pH2.0 and pH6.0 using pure hydrochloric acid. The solution is sterilized via filtration through a sterile 0.22 micron filter and stored in sealed sterile injection vials, each containing approximately 0.5 mg to approximately 30 mg active ingredient, depending on the final dosage unit desired in the sterile injection solution.

Sterile IV Solution:

A 5 mg/ml solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over 60 minutes.

Lyophilized powder for IV administration:

A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lypholized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 – 60 min.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention
5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be

dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Method of treating pharmacological disorders

The present invention also relates to a method of using the compounds or compositions described herein for the treatment or prevention of, or in the manufacture of a medicament for treating or preventing, mammalian hyper-proliferative disorders. This method comprises administering to a mammalian patient, including a human, in need thereof, an amount of a compound, a pharmaceutically acceptable salt thereof, or a composition of this invention that is effective to treat or prevent the disorder.

The present invention also relates to a method for using the compounds and compositions of this invention as prophylactic or chemopreventive agents for prevention of the mammalian hyper-proliferative disorders described herein. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, which is effective to delay or diminish the onset of the disorder.

The present compounds and compositions exhibit anti-proliferative activity and are thus useful to treat the disorders that are described below and/or otherwise known in the art. Hyper-proliferative disorders include diseases or conditions whose progression proceeds, at least in part, via proliferation.

Hyper-proliferative disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary

tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, and also exist with a similar etiology in other mammals which can also be treated by the administration of the compounds and/or pharmaceutical compositions of the present invention.

The utility of the compounds of the present invention can be illustrated, for example, by their activity *in vitro* in the *in vitro* tumor cell proliferation assay described below. The link between activity in tumor cell proliferation assays *in vitro* and anti-tumor activity in the clinical setting has been very well established in the art. For example, the therapeutic utility of taxol (Silvestrini et al. *Stem Cells* **1993**, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* **1995**, 6(3), 339), and topoisomerase inhibitors (Edelman et al. *Cancer Chemother. Pharmacol.* **1996**, 37(5), 385-93) were demonstrated with the use of *in vitro* tumor proliferation assays.

The following assays are two methods by which compound activity relating to treatment of the disorders identified herein can be determined.

Cellular Proliferation Assay (Plastic MTS) HCT116 cells are seeded at a density of 3000 cells per well in 100 uL DMEM universal growth medium in 96-well culture plates and incubated overnight at 37 °C in 5% CO_2 in a humidified incubator. T_0 MTS measurements are taken as described below. Cells are treated with test compounds serially diluted at10 uM, 5, 2.5, 1.25, 0.6uM, duplicate; Final concentration of DMSO in each well is 0.1% and incubated for 3 days at 37 °C in 5% CO_2 in a humidified incubator. Twenty micoliters of MTS reagent (CellTiter 96 Aqueous One Solution Cell Proliferation Assay) are added to each well and plates are incubated at 37 °C for 1 hour. Plates read in a Spectra MAX 250 Plate Reader at 490 nM. Percent inhibition is calculated by the following formula:

% inhibition = $1-(T_{72test}-T_0)/(T_{72ctrl}-T_0) \times 100$, where

T_{72test} = OD_{490nM} in the presence of test compound at T = 72h

T_{72ctrl} = OD_{490nM} in the absence of test compound at T = 72h

T_0 = OD_{490nM} in the absence of test compound at T = 0h

This assay may also be run using HT1080 or DLD-1 cell lines following the same procedure.

In vivo assay: Groups of female Ncr nude mice [Taconic Laboratories, NY] are inoculated with $3x10^6$ cells of HCT-116, a CRC xenograft on day 0. When tumors reach a

75 to 150 mm^3 in size (typically 6-8 days), animals are administered compounds of interest *p.o.* in a Cremaphor (12.5%; Sigma Aldrich, St. Louis, MO): Ethanol (12.5%): Saline (75%) vehicle for 14 days. The treatment volumes are 0.1mLl-test article/10g body weight. A group of 10 untreated animals is included to assess tumor response to test article vehicles. During the course of the study the animals tumor growth measurements and body weights are determined twice a week. All animals are observed for clinical signs daily and after compound administration. Tumor volume is calculated using the ellipsoid formula:

$$(D \times (d^2))/2$$

where,

D = diameter of the tumor at major axis

d = diameter of the tumor at minor axis

Representative compounds of this invention demonstrated an IC_{50} under 20 μM in assays such as those described above.

Based upon the above and other standard laboratory techniques known to evaluate compounds useful for the prevention and/or treatment of the diseases or disorders described above by standard toxicity tests and by standard pharmacological assays for the determination of the prevention and/or treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for prevention and/or treatment of each desired indication. The amount of the active ingredient to be administered in the prevention and/or treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the duration of treatment (including prophylactic treatment), the age and sex of the patient treated, and the nature and extent of the condition to be prevented and/or treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 300 mg/kg, and preferably from about 0.10 mg/kg to about 150 mg/kg body weight per day. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical

dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of administration and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional prevention and/or treatment tests.

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with other anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof.

For example, optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment and/or prevention of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin,

interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

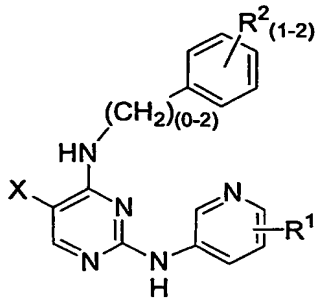
Other anti-hyper-proliferative agents suitable for use with the composition of this invention include but are not limited to other anti-cancer agents such as epothilone, irinotecan, raloxifen and topotecan.

It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

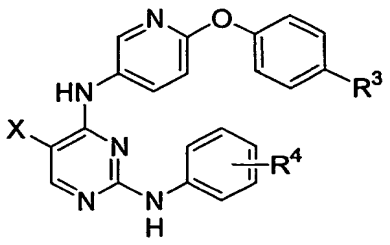
It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein. Numerous modifications and variations in the invention as described in the above illustrative examples are expected to occur to those skilled in the art and consequently only those limitations as appear in the appended claims should be placed thereon. Accordingly it is intended in the appended claims to cover all such equivalent variations which come within the scope of the invention as claimed.

WHAT IS CLAIMED IS:

1. A compound of Formula I(a) or I(b)



I(a)



I(b)

wherein

X is halo;

R^1 is selected from morpholinyl, NHC(O)(C_1-C_6)alkyl and O-phenyl wherein said phenyl is optionally substituted with a substituent selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, and CF_3;

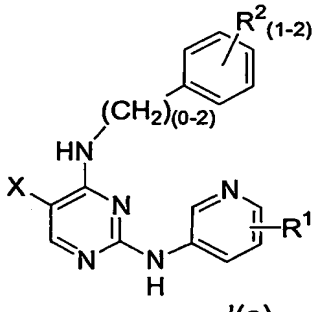
R^2 is in each instance independently selected from SO_2NH_2 and halo;

R^3 is selected from H, (C_1-C_6)alkoxy, CF_3 and halo;

R^4 is a substituent selected from C(O)OH, NHC(O)-phenyl, a five membered heterocycle, and imadazo[1,2-a]pyridinyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 comprising Formula I(a)



I(a)

wherein

X is halo;

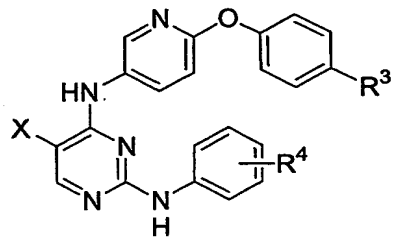
R^1 is selected from morpholinyl, NHC(O)(C_1-C_6)alkyl and O-phenyl wherein said

phenyl is optionally substituted with a substituent selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo, and CF_3;

R^2 is in each instance independently selected from SO_2NH_2 and halo;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 comprising Formula I I(b)



I(b)

wherein

X is halo;

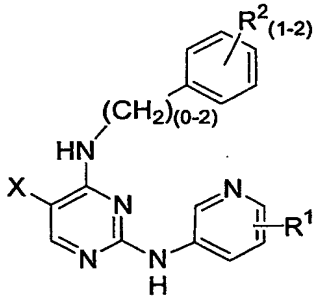
R^3 is selected from H, $(C_1\text{-}C_6)$alkoxy, CF_3 and halo;

R^4 is a substituent selected from C(O)OH, NHC(O)-phenyl, a five membered heterocycle, and imadazo[1,2-a]pyridinyl;

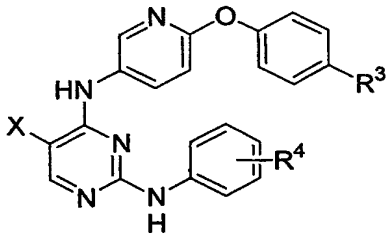
or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 wherein X is Br

5. A composition comprising a compound of Formula I(a) or I(b)



I(a)



I(b)

wherein

X is halo;

R^1 is selected from morpholinyl, NHC(O)$(C_1\text{-}C_6)$alkyl and O-phenyl wherein said phenyl is optionally substituted with a substituent selected from

(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, and CF_3;

R^2 is in each instance independently selected from SO_2NH_2 and halo;

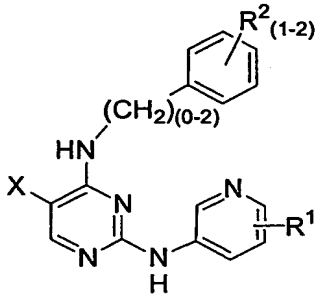
R^3 is selected from H, (C_1-C_6)alkoxy, CF_3 and halo;

R^4 is a substituent selected from C(O)OH, NHC(O)-phenyl, a five membered heterocycle, and imadazo[1,2-a]pyridinyl;

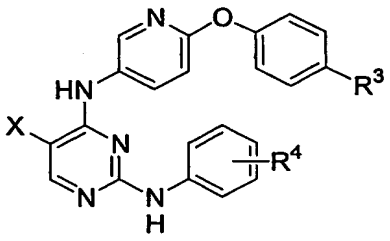
or a pharmaceutically acceptable salt thereof,

and at least one pharmaceutically acceptable carrier.

6. A method of treating a hyper-proliferative disorder comprising administering an effective amount of a compound of Formula I(a) or I(b)



I(a)



I(b)

wherein

X is halo;

R^1 is selected from morpholinyl, NHC(O)(C_1-C_6)alkyl and O-phenyl wherein said phenyl is optionally substituted with a substituent selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, and CF_3;

R^2 is in each instance independently selected from SO_2NH_2 and halo;

R^3 is selected from H, (C_1-C_6)alkoxy, CF_3 and halo;

R^4 is a substituent selected from C(O)OH, NHC(O)-phenyl, a five membered heterocycle, and imadazo[1,2-a]pyridinyl;

or a pharmaceutically acceptable salt thereof,

to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

Interna - pplication No
PCT/US 03/13604

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 19065 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 29 May 1997 (1997-05-29) claim 1 ---	1-6
Y	WO 00 39101 A (BREAULT GLORIA ANNE ;PEASE JANET ELIZABETH (GB); ASTRAZENECA UK LT) 6 July 2000 (2000-07-06) claim 1 ---	1-6
Y	WO 01 64656 A (PEARSON STUART ERIC ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) * Examples * claim 1 --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2003	01/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baston, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 03/13604

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 64654 A (BREAULT GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) claim 1	1-6
Y	WO 01 64655 A (BREAULT GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) claim 1	1-6
Y	WO 95 09852 A (CIBA GEIGY AG) 13 April 1995 (1995-04-13) claim 1	1-6
Y	EP 0 564 409 A (CIBA GEIGY AG) 6 October 1993 (1993-10-06) claim 1	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible] Application No
PCT/[illegible] 03/13604

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9719065 A	29-05-1997	AU	7631496 A	11-06-1997
		DE	69627179 D1	08-05-2003
		EP	0862560 A1	09-09-1998
		WO	9719065 A1	29-05-1997
		US	6235746 B1	22-05-2001
		US	5958935 A	28-09-1999
WO 0039101 A	06-07-2000	AU	1874300 A	31-07-2000
		BR	9916590 A	23-10-2001
		CA	2352896 A1	06-07-2000
		CN	1335838 T	13-02-2002
		EP	1140860 A1	10-10-2001
		WO	0039101 A1	06-07-2000
		JP	2002533446 T	08-10-2002
		NO	20013038 A	22-08-2001
		US	6593326 B1	15-07-2003
WO 0164656 A	07-09-2001	AU	3397901 A	12-09-2001
		BR	0108879 A	29-04-2003
		CA	2398887 A1	07-09-2001
		CN	1416423 T	07-05-2003
		EP	1278735 A1	29-01-2003
		WO	0164656 A1	07-09-2001
		NO	20024126 A	29-08-2002
WO 0164654 A	07-09-2001	AU	3395301 A	12-09-2001
		BR	0108841 A	06-05-2003
		CA	2399196 A1	07-09-2001
		CN	1406231 T	26-03-2003
		EP	1272477 A1	08-01-2003
		WO	0164654 A1	07-09-2001
		NO	20024154 A	28-10-2002
WO 0164655 A	07-09-2001	AU	3397601 A	12-09-2001
		BR	0108834 A	10-12-2002
		CA	2398685 A1	07-09-2001
		CN	1406230 T	26-03-2003
		EP	1268444 A1	02-01-2003
		WO	0164655 A1	07-09-2001
		NO	20024153 A	29-10-2002
WO 9509852 A	13-04-1995	AU	693804 B2	09-07-1998
		AU	7697594 A	01-05-1995
		CA	2148477 A1	13-04-1995
		WO	9509852 A1	13-04-1995
		EP	0672040 A1	20-09-1995
		JP	8504834 T	28-05-1996
		US	5521184 A	28-05-1996
		US	5543520 A	06-08-1996
EP 0564409 A	06-10-1993	AT	188964 T	15-02-2000
		AU	3569493 A	07-10-1993
		BR	1100739 A3	06-06-2000
		CA	2093203 A1	04-10-1993
		CN	1077713 A ,B	27-10-1993
		CZ	9300560 A3	16-02-1994
		DE	59309931 D1	24-02-2000
		DK	564409 T3	19-06-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat... Application No
PCT/US 03/13604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0564409 A		EP 0564409 A1	06-10-1993
		ES 2142857 T3	01-05-2000
		FI 931458 A	04-10-1993
		GR 3032927 T3	31-07-2000
		HU 64050 A2	29-11-1993
		IL 105264 A	11-04-1999
		JP 2706682 B2	28-01-1998
		JP 6087834 A	29-03-1994
		KR 261366 B1	01-08-2000
		LU 90908 A9	30-04-2003
		MX 9301929 A1	29-07-1994
		NO 931283 A	04-10-1993
		NZ 247299 A	26-07-1995
		PT 564409 T	30-06-2000
		RU 2125992 C1	10-02-1999
		SG 43859 A1	14-11-1997
		SK 28093 A3	06-04-1994
		US 5521184 A	28-05-1996
		ZA 9302397 A	04-10-1993